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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,071	01/09/2006	Zeev Smilansky	2488.016	2101

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EXAMINER	
BORIN, MICHAEL L	

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
07/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,071	SMILANSKY, ZEEV	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/21/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/18/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Response to restriction requirement filed 03/17/2008 is acknowledged. Applicant elected, without traverse, Group I. All previously pending claims, claims 1-85 are canceled, and claims related to the elected Group I are replaced with new claims 86-107.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No.08/030340, filed on 03/25/93.

The parent applications 07/839647 and 08/041647 were closely reviewed. It is noted that the parent application discloses examples 1-111; examples 112-123 were submitted in the application 08/041647. Correspondingly, the compounds disclosed in the examples 112-123 are entitled to the effective filing date 04/01/93.

The claim for priority under 35 U.S.C. 120 is objected to because it is not the first sentence of the specification. See 37 CFR 1.78(a)(2).

Information Disclosure Statement

3. Applicants' Information Disclosure Statement filed 04/18/2006 has been received and entered into the application. Accordingly, as reflected by the attached completed copies of forms PTO-1449, the cited references have been considered.

Sequence Listing

4. The Sequence Listing was approved by STIC for matters of form.

Specification

5. The specification is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See, for example, paragraphs [0020], [0115], [0216], [0276] of PreGrant publication. Applicant is requested to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 102 and 103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 86-95 are rejected under 35 U.S.C. 102(b) as anticipated by Rothschild et al (US patent 6210941) or Dirks et al. (Histochemistry and Cell Biology Volume 115, Number 1 / January, 2001, p. 3-11)

The instant claims are drawn to method for monitoring protein synthesis comprising:

- providing a system comprising a marker detectable through detection of electromagnetic radiation, the marker comprising
  - at least one labeled ribosome or a labeled fragment thereof, and
  - at least one labeled element selected from the group consisting of the ribosome or a fragment thereof, or tRNA and an amino acid; and
- detecting electromagnetic radiation signals emitted from the system in response to protein synthesis activity

Rothschild et al teach method of detecting monitoring method for monitoring protein synthesis comprising:

- providing a system comprising
  - a labeled tRNA (which reads on a labeled ribosome fragment) and

- at least one labeled amino acid; and

- detecting electromagnetic radiation signals emitted from the system in response to protein synthesis activity

See col. 5, lines 26-40; col. 21-22, claims 1-25.

With respect to claim 87, the system can be cell- or in vitro translation system. See Abstract, col. 7, bottom.

With respect to claims 89-92, the marker can be fluorescent. See col. 12, for example.

With respect to claims 91-93, in addition to measuring fluorescent signal, protein synthesis can be monitored based on energy transfer from one marker to another. See col. 18, second paragraph.

Dirks et al review applications of fluorescent methods for visualizing RNA processing in ribosomes (which is viewed as monitoring of protein synthesis). Dirks describes several approaches, such as the "classic" approach, in which one or more fluorochromed oligonucleotides are hybridized to their target RNA sequence; the molecular beacon approach wherein fluorescence is observed only when the molecular beacon probes hybridize to their target, the fluorescence resonance energy transfer (FRET) approach wherein two hybridization events have to occur to bring a donor and an acceptor molecule (*red dot*) in close proximity to allow energy transfer between the donor and acceptor (and thus, fluorescent emission light from the acceptor molecule is visible only when two different oligonucleotide probes hybridize on the same

mRNA target molecule. See Figure 3. For the latter, FRET, the reference teaches that it is expected that the detection of FRET can be further improved using fluorescence lifetime imaging (FLIM). By FLIM the decrease of fluorescence lifetime of the donor fluorophore is measured so that fluorescent background signals, which are still detected together with the FRET signals, can be easily recognized as such.

It is the Examiners position that all the elements of Applicant's invention with respect to the specified claims are instantly disclosed by the teaching of the reference cited above

7. Claims 86, 96-107 are rejected under 35 U.S.C.103(a) as unpatentable over Rothchild et al, or Dirks et al.

The references are applied as discussed.

With respect to claims 96-107 if there are any differences between Applicant's claimed method and that of the prior art, the differences would be appear minor in nature. Although the prior art do not teach the various combinations of signal acquisition and analysis as claimed, the nature of the problem to be solved – monitoring protein synthesis - would lead inventors to look at references relating to possible factors known to affect detection and identification of fluorescent signals of labeled ribosome components. Based on particular situation, it would be conventional and within the skill of the art to select and/or determine such result-oriented variables as appropriate conditions for signal measurement and acquisition (e.g., single *vs.* plural

ribosomes, measuring after preliminary irradiation, using FRET conditions, etc), as well as signal analysis (e.g., recording signal type and comparing to database information, finding matching database information, etc). One of ordinary skill in the art would have been motivated to combine all known factors with no change in their respective functions, and the combination would have yielded nothing more than predictable results of more comprehensive monitoring of protein synthesis.

8. Claims 86-107 are rejected under 35 U.S.C.103(a) as unpatentable over Kukhanova et. al . (Molecular Biology Reports. Volume 1, Number 7 / September, 1974, pages 397-400) in view of Odom et al. (Biochemistry. 1990 Dec 4;29(48):10734) or Paulsen et al. (Biochemistry , Vol. 25, no. 10, pp. 2749, 1986).

Kukhanova et. al teach fliuorescently labeled peptidyl-tRNA for monitoring protein synthesis. Fliuorescently labeled peptidyl-tRNA is viewed as a marker comprising a labeled ribosome fragment, tRNA, and a labeled amino acid. See Abstract. Although the reference does not describe monitoring protein synthesis, it teaches that peptidyl-tRNA having a fluorescent label of sufficient size and hydrophobicity in the peptide moiety of the molecule may be specifically bound to ribosomes and may act as peptide donors. See last paragraph.Thus, one skilled in tha art at the time the invention was made would be motivated to use fliuorescently labeled peptidyl-tRNA for monitoring protein synthesis.

Indeed , Odom et al. describe use of fliuorescently labeled peptidyl-tRNA to

measure the position and movement of an analogue of a nascent peptide and the amino acid stem of the tRNA during the peptidyl transferase reaction. Also, energy transfer was also measured from labeled peptidyl-tRNA to a fluorescent derivative of erythromycin (p. 10734, right column, bottom), or to cysteine sulfhydryl residue of either ribosomal protein S21 or L11 (p. 10734, left column, bottom).

Similarly, Paulsen et al teach monitoring of tRNA topography in the course of translocation (I. e., in the course of protein synthesis). The distances between the anticodon loops of fluorescent $tRNA^{Phe}$ bound to the E site and to either the A or the P site of poly(U)-programmed Escherichia coli ribosomes were measured by fluorescence energy transfer. See Abstract.

With respect to claims 96-107 if there are any differences between Applicant's claimed method and that of the prior art, the differences would be appear minor in nature. Although the prior art do not teach the various combinations of signal acquisition and analysis as claimed, the nature of the problem to be solved – monitoring protein synthesis - would lead inventors to look at references relating to possible factors known to affect detection and identification of fluorescent signals of labeled ribosome components. Based on particular situation, it would be conventional and within the skill of the art to select and/or determine such result-oriented variables as appropriate conditions for signal measurement and acquisition (e.g., single *vs.* plural ribosomes, measuring after preliminary irradiation, using FRET conditions, etc), as well as signal analysis (e.g., recording signal type and comparing to database information,

finding matching database information, etc). One of ordinary skill in the art would have been motivated to combine all known factors with no change in their respective functions, and the combination would have yielded nothing more than predictable results of more comprehensive monitoring of protein synthesis.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael Borin, Ph.D./
Primary Examiner, Art Unit 1631